



Cycle 3 2016 Funding Cycle

PCORI Funding Announcement Reopened: Clinical Strategies for Managing and Reducing Long-Term Opioid Use for Chronic Pain

Published October 4, 2016

Updated May 19, 2017

This PCORI Funding Announcement (PFA) applies to the funding cycle that closes on February 7, 2017, at 5 p.m. (ET). Application Guidelines, templates, and other resources are available at <http://www.pcori.org/2016-Cycle-3-Opioid-Management>.



About PCORI

The Patient-Centered Outcomes Research Institute (PCORI) is committed to transparency and a rigorous stakeholder-driven process that emphasizes patient engagement. PCORI uses a variety of forums and public comment periods to obtain public input to enhance its work. PCORI helps people make informed healthcare decisions and improves healthcare delivery and outcomes by producing and promoting high-integrity, evidence-based information that comes from research guided by patients and other stakeholders.

PCORI was authorized by Congress in 2010 as a nonprofit, nongovernmental organization. PCORI's purpose, as defined by our authorizing legislation, is to help patients, caregivers, clinicians, purchasers, policy makers, and other healthcare system stakeholders make better-informed health decisions by "advancing the quality and relevance of evidence about how to prevent, diagnose, treat, monitor, and manage diseases, disorders, and other health conditions."

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Overview

Published	October 4, 2016
Updated	May 19, 2017
Letter of Intent Due	November 1, 2016, by 5 p.m. (ET) Letters of Intent (LOIs) will be screened for responsiveness to this PCORI Funding Announcement (PFA) and fit to program goals. Only those applicants selected will be permitted to submit full applications. Notification of denial or approval to submit a full application will occur no later than December 2, 2016.
Summary	<p>The Patient-Centered Outcomes Research Institute (PCORI) seeks to fund studies that compare two or more alternatives for addressing the management and reduction of long-term opioid use for chronic pain.</p> <p>Proposed studies must address clinical and healthcare delivery choices faced by patients, their caregivers, clinicians, or delivery systems. Proposed studies must compare two or more active interventions. They must involve patient populations that are representative of the U.S. population, and they must be large enough to provide precise estimates of hypothesized effectiveness differences and to support evaluation of potential differences in treatment effectiveness in patient subgroups.</p> <p>For this solicitation, applicants are not required to demonstrate that patients and other stakeholders are already engaged as research team members at the time an application is submitted. However, applicants should outline how patients and other stakeholders will participate as partners in various phases of the proposed research, once awarded. Applicants should describe their plan to form a Study Advisory Committee (SAC)¹, or other appropriate engagement body, to ensure that a broad spectrum of patients and other stakeholders advise and assist the research team with refining the study questions, outcomes, and protocols. These patients and other stakeholders must include national or regional organizations that represent, at a minimum, patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. Additional representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts.</p> <p>Note that this funding program does not support applications to conduct cost-effectiveness analysis or systematic reviews. The proposed studies must address one or both of the priority research questions identified in the main body of the PFA.</p>
Applicant Resources	See http://www.pcori.org/2016-Cycle-3-Opioid-Management

¹ The intent of the SAC described in the PFA is to ensure that a broad spectrum of patients and other stakeholders advise and assist the research team with refining the study questions, outcomes, and protocols. These patients and other stakeholders must include national or regional organizations that represent—at a minimum—patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. Additional representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts. However, PCORI understands that engagement structures and approaches vary widely. Other engagement approaches, such as forming stakeholder groups, panels, task forces, working groups, and other bodies, or involving individual patient and other stakeholder partners in various ways, are also permissible to employ—either in addition to or instead of—the formation of the SAC. The SAC provision is not meant to require that a separate governance or advisory entity be established beyond the study governance and advisory structure the awardee has planned, if an applicant already has an approach for including the relevant and required patient and other stakeholder partners. For clarification in your application materials and merit review purposes, please indicate which body or structure is filling the SAC requirements, including the requirements for in-person meetings at least two times per year and appropriate budgeting.



Key Dates	<p>PCORI Online System Opens: October 4, 2016</p> <p>Applicant Town Hall Session: October 11, 2016, 12:30 p.m. – 1:30 p.m. (ET)</p> <p>LOI Deadline: November 1, 2016, by 5 p.m. (ET)</p> <p>LOI Status Notification: December 2, 2016</p> <p>Application Deadline: February 7, 2017, by 5 p.m. (ET)</p> <p>Merit Review Dates: April 2017</p> <p>Awards Announced: September 12, 2017</p> <p>Earliest Project Start Date: November 2017</p>
Maximum Project Budget (Total Direct Costs)	\$10 million
Maximum Research Project Period	3–5 years
Funds Available Up To	\$19 million
Eligibility	<p>Applications may be submitted by any private-sector research organization, including any nonprofit or for-profit organization; any public-sector research organization, including any university or college hospital or healthcare system; any laboratory or manufacturer; or any unit of local, state, or federal government. The Internal Revenue Service must recognize all U.S. applicant organizations. Nondomestic components of organizations based in the United States and foreign organizations may apply as long as there is demonstrable benefit to the U.S. healthcare system and U.S. efforts in the area of patient-centered research can be shown clearly. Organizations may submit multiple applications for funding. Individuals are not permitted to apply.</p>
Review Criteria	<ol style="list-style-type: none"> 1. Potential for the study to fill critical gaps in evidence 2. Potential for the study findings to be adopted into clinical practice and improve delivery of care 3. Scientific merit (research design, analysis, and outcomes) 4. Investigator(s) and environment 5. Patient-centeredness 6. Patient and stakeholder engagement
Contact Us	<p>Programmatic Inquiries: Contact the PCORI Helpdesk via email (sciencequestions@pcori.org) or phone (202-627-1884), or complete the Research Inquiry Form (http://www.pcori.org/content/research-inquiry). PCORI will provide a response within three business days. However, we cannot guarantee that all questions will be addressed in a timely fashion when the inquiry is made three or fewer business days before an LOI or application deadline.</p> <p>Administrative, Financial, or Technical Inquiries: Contact the PCORI Helpdesk at pfa@pcori.org. PCORI will provide a response within two business days. Note that during the week of the application deadline, response times may exceed two business days. One week before an application deadline, applicants may also call the PCORI Helpdesk (202-627-1885). Applicants are asked to plan accordingly. It is the applicant’s responsibility to submit the application on or before the application deadline.</p>
Other	<p>Deadlines are at 5 p.m. (ET). If a deadline falls on a weekend or federal holiday, the deadline will be the following Monday or the next day after the federal holiday.</p>

NOTE FOR THIS REOPENED PFA:

- Given the policy importance and the evidentiary need, this PFA has been reopened.
- Applicants are advised to review the awards that PCORI has [funded](#) through the original announcement to ensure that their proposed research complements those projects.
- The scientific background and two priority research questions remain unchanged from the PFA on Clinical Strategies for Managing and Reducing Long-Term Opioid Use for Chronic Pain issued for Cycle 3-2015.
- Changes in the PFA include:
 - i. Minor updates to the Outcomes section on page 6.
 - ii. As noted on page 6, the total funds available for this announcement are \$19 million.
 - iii. In Section IV on Merit Review, a New Criterion 4 has been added and the section has been updated.
 - iv. The Replication and Reproducibility of Research and Data-Sharing Plan requirement during the application phase has been removed.
 - v. Links to new [PCORI Policy on Data and Safety Monitoring Plans for PCORI-Funded Research](#) and [Process for Peer Review of Primary Research and Public Release of Research Findings](#) are now provided.

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I. Introduction

Summary of Program

The Patient-Centered Outcomes Research Institute (PCORI) is reopening this funding initiative to support patient-centered comparative clinical effectiveness research (CER) that addresses important questions regarding clinical strategies for managing and reducing long-term opioid use for chronic pain. Through this PCORI Funding Announcement (PFA), PCORI seeks to fund studies that have a sufficient sample size to address the research questions noted below and that will generate information that is readily generalizable to the broader population.

Competitive applications must directly address at least one of the two priority research questions described in this PFA.

The two priority research questions are:

- Among patients with chronic noncancer pain on moderate/high-dose long-term opioid therapy, what is the comparative effectiveness of strategies for reducing/eliminating opioid use while managing pain?
- Among patients with chronic noncancer pain on moderate/low-dose long-term opioid therapy, what are the comparative effectiveness and harms of strategies used to limit dose escalation?

In addition, applications should:

- Focus on patient populations with chronic noncancer pain who have used opioids for longer than three months. All chronic pain disorders outside of cancer pain or pain at end of life are considered chronic noncancer pain.
- Have strong endorsement and study participation by relevant patient organizations, professional organizations, and payer or purchaser organizations.
- Take place within typical clinical care and community settings.
- Have a sufficiently large study population to enable precise estimates of effect sizes and to support evaluation of potential differences in intervention effectiveness in patient subgroups such as those with comorbid mental health disorders or past/present substance abuse, and types of pain.
- Compare the effectiveness² of two or more alternatives for improving patient-centered outcomes.

Background

Chronic pain, defined as pain lasting longer than three months or past the time of normal healing, is

² Effectiveness is the extent to which an intervention does more good than harm in a broad mix of patients when provided under the usual circumstances of healthcare practice (modified from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1116525/>).

highly prevalent and a leading cause of disability and decreased quality of life.^{3,4,5} The Institute of Medicine estimates that more than 100 million Americans—approximately one-third of the U.S. population—suffer from chronic pain. The societal costs of pain top \$560 billion per year from medical expenses, disability, and lost wages and productivity.⁶ Opioids are widely accepted for treating cancer-related chronic pain in the palliative care setting; however, their use for other types of chronic pain remains controversial.⁷ Despite the stark absence of high-quality evidence to demonstrate the safety and effectiveness of long-term opioid therapy for managing chronic pain, between five million and eight million Americans use opioids for chronic pain management.^{5,6} In the last 20 years, opioid prescriptions have increased by 300 percent, with an estimated 201.5 million dispensed in 2009.^{8,9} Recent evidence reviews have also found that most clinical and policy decisions on the use of long-term opioid therapy for chronic pain—including U.S. and Canadian guidelines recommendations—are based on weak or insufficient evidence and consensus opinion.^{7,9,10}

Although there is little evidence regarding the effectiveness of chronic opioid therapy in improving function and pain, mounting evidence suggests that opioids may be associated with important harms, including overdose, abuse, addiction, and diversion.^{11,12,13,14,15,16,17} From 2001 to 2013, there was a three-fold increase in the total number of deaths from prescription opioids; in 2010, there were more than 600,000 emergency department visits due to opioid misuse and abuse.^{14,18} Other common adverse

³ Ballantyne, JC, Shin, NS. Efficacy of opioids for chronic pain: a review of the evidence. *Clinical J Pain*. 2008;24(6):469–78.

⁴ Eriksen, J, Sjogren, P, Bruera, E, Rasmussen, NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain*. 2006; 125(1–2):172–9.

⁵ International Association for the Study of Pain, Subcommittee on Taxonomy. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. *Pain Suppl*. 1986; 3: S1–226.

⁶ Institute of Medicine. Relieving pain in America: a blueprint for transforming prevention, care, education, and research. Washington, DC: National Academies Press; 2011.

⁷ Chou, R, Fanciullo, GJ, Fine, PG, Adler, JA, Ballantyne, JC, Davies, P, Donovan, MI, Fishbain, DA, Foley, KM, Fudin, J, Gilson, AM, Kelter, A, Mauskop, A, O'Connor, PG, Passik, SD, Pasternak, GW, Portenoy, RK, Rich, BA, Roberts, RG, Todd, KH, Miaskowski, C; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel; American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009; 10:113–30.

⁸ National Institute of Drug Abuse. Opioid use for chronic pain infographic. Accessed at <http://www.drugabuse.gov/related-topics/pain> on 8 March 2015.

⁹ Chou, R, Deyo, R, Devine, B, Hansen, R, Sullivan, S, Jarvik, JG, Blazina, I, Dana, T, Bougatsos, C, Turner, J. The effectiveness and risks of long-term opioid treatment of chronic pain. Evidence report/technology assessment no. 218. (Prepared by the Pacific Northwest Evidence-based Practice Center under contract no. 290-2012-00014-I). AHRQ publication no. 14-E005-EF. Rockville (MD): Agency for Healthcare Research and Quality; 2014. Accessed at www.effectivehealthcare.ahrq.gov/ehc/products/557/1971/chronic-pain-opioid-treatment-report-141007.pdf on 8 March 2015/.

¹⁰ Furlan, AD, Reardon, R, Weppler C. Opioids for chronic noncancer pain: a new Canadian practice guideline. *CMAJ*. 2010;182(9):923-930. PMID 20439443.

¹¹ Starrels, JL, Becker, WC, Weiner, MG, Li, X, Heo, M, Turner, BJ. Low use of opioid risk reduction strategies in primary care even for high-risk patients with chronic pain. *J Gen Intern Med*. 2011; 26(9):958–64.

¹² Gomes, T, Redelmeier, DA, Juurlink, DN, Dhalla, IA, Camacho, X, Mamdani, MM. Opioid dose and risk of road trauma in Canada: a population-based study. *JAMA Intern Med*. 2013; 173(3):196–201.

¹³ Deyo, RA, Smith, DH, Johnson, ES, Tillotson, CJ, Donovan, M, Yang, X, Petrik, A, Morasco, BJ, Dobscha, SK. Prescription opioids for back pain and use of medications for erectile dysfunction. *Spine*. 2013; 38(11):909–15.

¹⁴ Substance Abuse and Mental Health Services Administration. The DAW Report: Highlights of the 2010 Drug Abuse Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits. Rockville, MD: Center for Behavioral Health Statistics and Quality; 2012.

¹⁵ Starrels, JL, Becker, WC, Alford, DP, Kapoor, A, Williams, AR, Turner, BJ. Systematic review: treatment agreements pain and urine drug testing to reduce opioid misuse in patients with chronic pain. *Ann Intern Med*. 2010; 152:712–20.

¹⁶ Bohnert, AS, Valenstein, M, Bair, MJ, Ganoczy, D, McCarthy, JF, Ilgen, MA, Blow, FC. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA*. 2011; 305(13): 1,315–21.

¹⁷ Volkow, ND, McLellan, TA. Curtailing diversion and abuse of opioid analgesics without jeopardizing pain treatment. *JAMA*. 2011; 305(13): 1,346–7.

¹⁸ National Institute on Drug Abuse. Statistics. Accessed at <http://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates> on 8 March 2015.

events from opioid therapy include sedation, impaired cognitive function, depression, constipation, and bladder dysfunction.^{9,19}

Although findings from randomized trials do suggest that opioids may provide pain relief in the short term, most placebo-controlled randomized controlled trials (RCTs) were shorter than 16 weeks.⁹ No large-scale studies have assessed strategies for managing and reducing chronic opioid use in a real-world setting. Additional rigorous research is needed to inform physician and patient decision making. Results from comparative studies have the potential to be rapidly implemented, affect clinical decision making, and guide clinician opioid-prescribing practices, resulting in a reduction in the harms and risks associated with long-term opioid therapy for the treatment of chronic pain.^{9,20}

Evidence Gap

A recent systematic review commissioned by the Agency for Healthcare Research and Quality (AHRQ) for the National Institutes of Health (NIH) Pathways to Prevention Workshop on the effectiveness and risks of long-term opioid therapy identified large and persistent evidence gaps with regard to the use of chronic opioid therapy. Given the lack of evidence supporting the long-term use of opioids, clinical decision making is primarily guided by experience rather than evidence.

Specifically, the review found that no studies of opioid or non-opioid alternative therapies (e.g., physical therapy, behavioral therapy, or proven complementary and alternative medicine approaches) have evaluated outcomes related to pain, function, or quality of life for longer than one year.^{9,21} Likewise, no studies examined the comparative effectiveness of opioids plus non-opioid interventions versus opioids or non-opioid interventions alone for the patient-centered outcomes (i.e., pain, function, quality of life).

Per the AHRQ Evidence Review, there is also limited evidence on the effectiveness of different opioid dosing strategies.^{9,21} Of the few studies in this area, there was only one small study of 10 participants on decreasing doses or tapering off versus continuation, but results from the crossover trial cannot be applied to the general population.^{9,21,22} Two studies focused on different tapering protocols and strategies on measures related to pain, function, quality of life, withdrawal, and likelihood of opioid cessation, but were classified as poor-quality, nonrandomized, prospective observational studies. Neither study evaluated effects of discontinuing opioids on pain, function, quality of life, or withdrawal symptoms.^{9,21,23,24} All studies had methodological shortcomings and showed no clear differences on outcomes related to pain and function. In addition, there were no studies on the effects of decreasing

¹⁹ Furlan, AD, Sandoval, JA, Mailis-Gagnon, A, Tunks, E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. *CMAJ*. 2006; 174(11): 1,589–94.

²⁰ Chou, R, Ballantyne, JC, Fanciullo, GJ, Fine, P. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American Pain Society and American Academy of Pain Medicine Clinical Practice Guideline. *J Pain*. 2009; 10:147–59.

²¹ Chou, R, Turner, JA, Devine, EB, Hansen, RN, Sullivan, SD, Blazina, I, Dana, T, Bougatsos, C, Deyo, RA. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention workshop. *Ann Intern Med*. 2015; 162:276–86.

²² Cowan, DT, Wilson-Barnett, J, Griffiths, P, et al. A randomized, double-blind, placebo controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. *Pain Med*. 2005;6(2):113–21. PMID: 15773875.

²³ Ralphs, JA, Williams, AC, Richardson, PH, et al. Opiate reduction in chronic pain patients: a comparison of patient-controlled reduction and staff controlled cocktail methods. *Pain*. 1994;56(3):279–88. PMID: 8022621.

²⁴ Tennant, FS, Jr., Rawson, RA. Outpatient treatment of prescription opioid dependence: comparison of two methods. *Arch Intern Med*. 1982;142(10):1845–7. PMID: 6181749.

opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and withdrawal for patients on long-term opioid therapy.^{9,21} Finally, no studies have examined how treatment effectiveness may vary based on cause of pain, patient demographics, or comorbidities.^{9,21}

The systematic review concluded that there were insufficient data on the long-term effectiveness of chronic opioid therapy. However, increasing evidence does support the increased risk for harm associated with the use of chronic opioid therapy. A number of studies have noted an association between higher opioid doses and risk of an opioid use disorder and overdose. The likelihood for developing an opioid use disorder increased 122-fold for patients on chronic high-dose opioids (> 120 mg/day morphine equivalent dose [MED]) compared to patients who were not prescribed opioids.^{9,25,26} Overdose risk increased by almost 1.5 at doses between 20 to 49 mg/day MED and increased almost nine-fold for doses greater than 100 mg/day MED.^{21,25^{27,28,29}} These studies also identified that, for patients on doses between 50–100 mg/day MED, the risk of overdose was 2.2 to 4.6 times higher than it was at lower doses. Research also suggests an association between patients on higher-dose opioids and mental health disorders, substance use disorder, and opioid misuse.^{25,30}

Based on the findings from the systematic review, additional research is needed to understand the long-term patient outcomes, the risks of opioid abuse, and the effects of different opioid prescription methods and risk mitigation strategies. Importantly, the review also identified key questions regarding the effectiveness of treatment options for patients with comorbid disorders, including mental health disorders and past or current substance use disorders and different causes of pain.

Research Topic Prioritization

PCORI relies on input from multiple stakeholders to set its research priorities. Members of its advisory panels include patients, clinicians, researchers, purchasers, payers, industry, and other healthcare stakeholders. Staff identified the use of long-term opioids for chronic pain as an important topic, which PCORI's Advisory Panel on Assessment of Prevention, Diagnosis, and Treatment Options then ranked as a high priority when it met on April 9, 2015. PCORI then convened a large multi-stakeholder workshop on June 9, 2015, to provide further input on whether specific opioid CER questions could be addressed by PCORI-funded research. Approximately 47 invited stakeholders attended in person. The meeting was open to the public via teleconference and webinar.

Workshop participants submitted questions for discussion prior to the meeting, and PCORI staff refined these questions to yield a total of 24 comparative effectiveness questions. Two opioid panels reviewed

²⁵ Washington State Agency Medical Directors' Group. *Interagency guideline on prescribing opioids for pain*. <http://www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf>. Published May 2015. Accessed June 29, 2015.

²⁶ Edlund, MJ, Martin, BC, Russo, JE, et al. The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain. *Clin J Pain*. 2014; 30(7):557-6.

²⁷ Dunn, KM, Saunders, KW, Rutter, CM, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. *Ann Intern Med* 2010; 152:85-92.

²⁸ Bohnert, AS, Valenstein, M, Bair, MJ, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. *JAMA* 2011; 305:1315-21.

²⁹ Zedler, B, Xie, L, Wang, L, et al. Risk Factors for Serious Prescription Opioid-Related Toxicity or Overdose among Veterans Health Administration Patients. *Pain Med* 2014; 15:1911-29.

³⁰ Martin, BC, Fan, MY, Edlund, MJ, Devries, A, Braden, JB, Sullivan, MD. Long-term chronic opioid therapy discontinuation rates from the TROUP study. *J Gen Intern Med* 2011; 26:1450-7.

the questions. Panel 1 focused on pharmacologic treatment options and dosing strategies, while Panel 2 focused on studies that include multimodal therapy, risk mitigation strategies, and opioid dependency.

Participants discussed, revised, and ranked the questions during breakout sessions at the workshop. PCORI staff used the results of this ranking to help inform its selection of two high-priority research questions. Staff further refined and modified the draft questions in consultation with the Scientific Oversight Committee members. The PCORI Board of Governors (Board) reviewed and approved these questions as the basis for this funding announcement.

Based on the key gaps noted above, input from our large multi-stakeholder workshop, and the Scientific Oversight Committee, PCORI is interested in applications that respond to the following comparative effectiveness questions:

The two priority research questions are:

- Among patients with chronic noncancer pain on moderate/high-dose long-term opioid therapy, what is the comparative effectiveness of strategies for reducing/eliminating opioid use while managing pain?
- Among patients with chronic noncancer pain on moderate/low-dose long-term opioid therapy, what are the comparative effectiveness and harms of strategies used to limit dose escalation?

Priority Research Questions

Applications should propose large pragmatic studies, preferably RCTs or, as necessary and justified, well-designed observational studies that address one or both of the following two priority research questions. Pragmatic trials are designed to maximize applicability of the study's results in routine clinical practice. They are conducted in routine clinical care settings, and in many cases, the sample size should be relatively large, in part to be able to demonstrate differences in comparative effectiveness across different patient subgroups. They should impose fewer constraints on usual practice than traditional RCTs. Please note that applicants are advised to review the [two awards](#) that PCORI has funded through the original announcement to ensure that their proposed research complements those projects and strengthens the evidence base.

Among patients with chronic noncancer pain on moderate/high-dose long-term opioid therapy, what is the comparative effectiveness of strategies for reducing/eliminating opioid use while managing pain?

PCORI is interested in receiving applications that propose to compare distinctly different clinical strategies, which could include structured dose reduction protocols and non-opioid therapies (pharmacological or nonpharmacological options) among patients on moderate/ high-dose long-term opioid therapy. Given that the definition of moderate- to high-dose opioid therapy has varied in previous guidance (e.g., 90mg MED, 100mg MED, to 120 mg MED), applicants should provide a strong rationale along with supporting evidence for the selection of a particular threshold definition. Studies that integrate pharmacological options may include nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, mood stabilizers, and others. Nonpharmacological options may include physical therapy, behavioral therapy, commonly used complementary and alternative medicine approaches, and

others. As appropriate and necessary, studies should include risk mitigation strategies across all treatment comparators. Applicants may propose alternative non-opioid interventions not noted above.

Applicants should provide a convincing explanation for the relevance of the treatment options being compared in the proposed study, citing evidence gaps that are justified on the basis of systematic reviews. PCORI is interested in studies that include important comorbidities such as mental health disorders and past or current substance use disorders. Other key patient subgroups include groupings based on the source or type of pain. Importantly, applications must include efficacy data and/or information indicating that the interventions are commonly used in clinical practice. Applicants must also provide a clear justification that the interventions represent a realistic choice currently faced by patients and clinicians.

Among patients with chronic noncancer pain on moderate/low-dose long-term opioid therapy, what are the comparative effectiveness and harms of strategies used to limit dose escalation?

PCORI is interested in studies that compare alternative strategies for limiting dose escalation among patients on moderate/low-dose chronic opioid therapy. We encourage comparisons that may include combinations of non-opioid interventions, opioid rotation, dosing strategies, or risk mitigation strategies. Applicants should provide a convincing explanation for the relevance of the clinical options being compared, including efficacy data and/or information indicating that the interventions are commonly used in clinical practice. Subgroup analyses should include important comorbidities such as mental health disorders, past or current substance use disorders, and type of pain.

Outcomes (Revised)

For both of the priority questions, applicants should consider a broad range of outcomes that are important to patients. Studies must be adequately powered to assess the following outcome measures at 12 months: opioid dose change, pain control, and function. Where applicable, primary outcome measures should be based on validated and widely used measurement scales. Other key outcomes include health-related quality of life, opioid misuse, safety, mortality, medical side effects of treatment, depression, and health service utilization. Applicants should consider a minimum one-year follow-up for primary and secondary outcome measures.

Funds Available (Revised)

PCORI seeks to fund studies that address each of the two priority questions but does not commit to such. PCORI will consider the merit of each submitted application and its responsiveness to each priority question, as well as programmatic requirements and portfolio balance, when making final funding recommendations.

PCORI has devoted up to \$19 million in total costs under this reopened PCORI PFA to fund high-impact studies related to the management of long-term opioid therapy for chronic pain. The proposed budget for individual studies may range up to \$10 million in total direct costs as appropriate, depending on the specific priority research question or questions the study proposes to address. The maximum project period is five years.

Given the significant implementation costs associated with some interventions, the applications must

specifically address—in the context of the proposed studies—the support from payers, health plans, industry sponsors, or others in covering the study interventions and non-study, protocol-related clinical costs and services rendered in the care processes. Of particular concern would be different levels of co-payment between two arms in a comparative study. Ideally, cost-sharing barriers will be eliminated or equalized in the study arms. If the study design does not allow this, the applicant should describe why and discuss how differences in co-payment costs will be accounted for in the analysis of the study's findings.

It is expected that project budgets and duration will vary substantially, depending on the topic and approach selected, needs for recruitment or primary data collection, length of follow-up, and analytic complexity. PCORI seeks efficient studies, such as those that take advantage of large populations already under observation; registries; research cooperatives; and the supportive involvement of delivery systems or health plans to enhance recruitment, data collection, and coverage of intervention-related costs. A prolonged recruitment period is not an acceptable rationale for longer studies. Funding requests to develop or build upon initial collaboration between researchers and patient/stakeholder groups are also not appropriate for this PFA.

II. Guidance for Preparing Applications

Specific Requirements

The proposed study should strive to meet the following requirements:

- Focus on a comparative effectiveness question that is important to patients and other decision makers.
- Address a research gap that has been substantiated by an existing (recent or updated), rigorously conducted systematic review or emphasized by an official professional society's clinical practice guideline.
- Demonstrate consultation with patients and other stakeholders or their representative groups, or reference previously documented decisional dilemmas to determine if the study is answering a critical question—one that, if adequately answered, would substantially improve decision making.
- Receive endorsement by relevant patient organizations, clinician organizations, payer or purchaser consortia, or life sciences industry representatives as potentially answering a critical question—one that, if adequately answered, would substantially improve decision making.
- Propose a sample size that is sufficiently large to allow for precise estimation of hypothesized effect sizes. The sample size must also support testing of *a priori* hypotheses related to potential differences in effectiveness among relevant patient subgroups (Heterogeneity of Treatment Effect, or HTE).
- Examine diverse populations receiving care in real-world settings.
- Have strong interest from and support of host delivery systems and clinical care settings.

- Specify broad and simple eligibility criteria that will allow wide generalization of results while attending appropriately to ethical concerns of excess risk in some patient subgroups.
- As applicable, compare interventions that are known to be efficacious, effective, or commonly used and that can be implemented in real-world settings.
- Include patient-reported outcomes (PROs) as primary outcomes, when appropriate.
- Provide preliminary evidence of the potential for efficient recruitment, high participation rates, and appropriate oversight by local or centralized Institutional Review Boards (IRBs), including plans for streamlining or waiving individual informed consent in cases of low-risk interventions. PCORI believes that the intensity of oversight and the complexity of informed consent procedures should be closely related to the degree of risk from study participation. Applicants must address this issue and present evidence that the study will not encounter significant barriers to recruitment or participation. The relevant IRBs make the final determination of the adequacy of informed consent procedures and participant protections.
- Adhere to all applicable [PCORI Methodology Standards](#).³¹ The full application will require the applicant to identify the standards appropriate to the proposed study and describe how the study team plans to address each standard.
- In the case of RCTs, also adhere to current best practices (standardized inclusion or exclusion criteria; proper randomization; techniques to minimize potential for missing data; and appropriate safety monitoring, including establishment of a Data and Safety Monitoring Board [DSMB] or indication of why such a board is unnecessary).
- For observational studies, employ rigorous designs that can address concerns related to causal inferences about the relative effectiveness of different strategies on patient-centered outcomes. Applications will need to make a clear conceptual and analytical connection between interventions, comparators, and patient-centered outcomes. Investigators should carefully consider and justify the appropriate observational design for their question, which may include opportunistic, natural experiments or other observational research approaches that use longitudinal, quasi-experimental study designs. Proposals using cross-sectional or simple pre-post designs are discouraged.
- To carry out CER studies, readily adopt the findings in a real-world setting, and maximize the efficient use of resources, applicants must prevent these trials from becoming more complex and onerous than necessary. PCORI encourages the applicant to be creative and consider the following innovative strategies, as appropriate and feasible:
 - Be prepared to identify and engage with major patient and stakeholder organizations that would implement study findings, as well as with existing local communities of patients and care providers to refine the research questions and study protocol, help monitor progress, and disseminate the findings.

³¹ Available at pcori.org/research-we-support/research-methodology-standards/.

- Consult with patients and other stakeholders on their decisional dilemma and evidence needs, or reference previously documented decisional dilemmas in preparation for submitting Letters of Intent (LOIs) and the full applications.
- Describe carefully the pertinent evidence gaps and why the project questions represent decisional dilemmas for patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. Similarly, applicants should document why project outcomes are especially relevant and meaningful endpoints for patients and other stakeholders. Minimize disruption to participants' daily routines (e.g., minimize participant visits intended for study assessment purposes; capture PROs during office visits, electronically, or by phone).
- Design the study so that the conduct can integrate with routine clinic or office operations as seamlessly as possible.
- Use efficient methods to obtain participant consent while still meeting ethical and legal requirements.
- Capitalize on the existing electronic health records (EHRs) and other computerized information to identify and recruit eligible patients, monitor study conduct and patient safety, and collect study outcomes information. PCORI specifically encourages applications that use the National Patient-Centered Clinical Research Network (PCORnet) infrastructure.
- If data standardization and interoperability across study sites have not already been accomplished, develop methods that will enhance the standardization of data that are accessed from different EHR systems.

Nonresponsiveness

Applications will be considered nonresponsive to this PFA if the proposed research:

- Aims to establish the efficacy of a new intervention
- Conducts a cost-effectiveness analysis in the form of dollar-cost per quality-adjusted life-year to compare two or more alternatives
- Directly compares the costs of care between two or more alternative approaches
- Measures the relative costs of care of two or more alternative approaches as the primary criteria for choosing the preferred alternative
- Conducts studies of the natural history of disease, instrument development, pharmacodynamics, and fundamental science of biological mechanisms
- Proposes a pilot study intended to inform larger efforts
- Develops clinical prediction or prognostication tools
- Develops clinical practice guidelines

Applications may measure and report use of any or all health services, but may not employ direct measurements of care costs.

PCORI does have an interest, however, in studying conditions that lead to high costs to the individual or to society. Thus, PCORI is also interested in studies that do the following:

- Address cost-related issues, such as the resources needed to replicate or disseminate a successful intervention.
- Evaluate interventions to reduce health-system waste or increase health-system efficiency.

Applications that include studies of these issues without using cost-effectiveness analyses or comparing the costs of alternatives are considered responsive.

Features of Patient-Centered Outcomes Research

PCORI funds patient-centered outcomes research (PCOR), which helps people and their caregivers communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value of healthcare options. This research:

- Assesses the benefits and harms of preventive, diagnostic, therapeutic, or palliative care to inform decision making, highlighting the choices that matter to people
- Is inclusive of an individual's preferences, autonomy, and needs, focusing on outcomes that people notice and care about (including survival, functioning, symptoms, and health-related quality of life)
- Incorporates a wide variety of settings and diversity of participants to address individual differences and barriers to implementation and dissemination
- Directly compares clinical interventions that are available in the clinical settings
- Obtains stakeholder perspectives to address the burdens to individuals, availability of services, and technology and personnel requirements

Leveraging Existing Resources

PCORI encourages investigators to propose studies that leverage existing resources, such as adding PCOR to an existing large clinical trial or analyzing existing large databases that contain valuable and relevant information that may be used to answer important CER questions. Studies that leverage existing research networks or consortia that would facilitate the conduct of large, multi-site studies called for in this funding announcement are of interest.

Preliminary Data and Use of Accepted Measures

PCORI encourages investigators to design their research using valid patient-centered outcomes measures. Include preliminary data that support using the proposed measures in the study population. We encourage investigators to consider those measures described in the [Patient-Reported Outcomes Measurement Information System \(PROMIS\)](#).³²

³² Available at <http://nihpromis.org/>.

Methodological Considerations

Regardless of study design, applications must adhere to all relevant **PCORI Methodology Standards**.³³ These include 47 individual standards that fall into 11 categories. The first five categories are crosscutting and relevant to most PCOR studies. Researchers should refer to all of these standards when planning and conducting their research projects. These crosscutting categories are:

1. Standards for Formulating Research Questions
2. Standards Associated with Patient-Centeredness
3. Standards on Data Integrity and Rigorous Analyses
4. Standards for Preventing and Handling Missing Data
5. Standards for Heterogeneity of Treatment Effect (HTE)

Six other standards categories will be applicable to particular study designs and methods. The standards in each of these categories should be used as guidance when they are relevant to a study. These categories are:

1. Standards for Data Registries
2. Standards for Data Networks as Research-Facilitating Infrastructures
3. Standards for Causal Inference Methods
4. Standards for Adaptive and Bayesian Trial Designs
5. Standards for Studies of Diagnostic Tests
6. Standards for Systematic Reviews

Most of these standards are minimal. The PCORI Methodology Standards reflect practices that should be followed in all cases, and all deviations need to be explained and well justified. Additional best practices—including relevant guidelines for conducting clinical trials developed by other organizations—should be addressed in the application for PCORI funding. To help reviewers quickly identify the adherence to a particular standard, applicants must cite each relevant PCORI Methodology Standard within their applications as the standard is being addressed. For example, when applicants describe the need for their proposed study in the Background section, they should indicate the particular standard to identify evidence gaps in parentheses, such as “(RQ-1).”

Applicants should specifically discuss their capacity to measure such factors as differential adherence to chosen treatments (or participation in intervention programs) that could create or explain apparent differences in the effectiveness of the alternative interventions being compared in clinical populations.

Patient and Stakeholder Engagement

PCORI encourages all applicants to outline how patients and other stakeholders will participate as partners in various phases of the proposed research. Before completing this section of the Research

³³ Available at pcori.org/research-we-support/the-pcori-methodology-report/.

Strategy, applicants are encouraged to review [PCORI's Engagement Rubric](#),³⁴ which can be found in the PCORI Funding Center. Applicants should also review the PCORI Methodology Standards Associated with Patient-Centeredness and [PCORI's Sample Engagement Plans](#).³⁵ The rubric and Sample Engagement Plans are not intended to be comprehensive or prescriptive; instead, they provide a variety of examples to incorporate engagement, where relevant, into the research process.

Applicants are expected to consult with patients and other stakeholders on their decisional dilemma and evidence needs or to reference previously documented decisional dilemmas in preparation for the submission of LOIs and applications. To describe the decisional dilemma, state the specific clinical decision(s) or treatment choice(s) confronted by the decision makers and explain how the findings from the proposed research will inform those decisions. State why this decision—such as choosing a specific medication, surgical approach, or care delivery strategy to treat a condition or manage a specific population—is important to patients. Document the uncertainty patients and other stakeholders face in making this decision. Identify the patients and other stakeholders you consulted in determining that the proposed study addresses their evidentiary needs for decision making, and indicate your commitment to continue engaging them actively in the conduct of the study. Similarly, applicants should document how the project outcomes are especially relevant and meaningful endpoints to patients and other stakeholders.

For this PFA, applicants are not required to demonstrate that patients and other stakeholders are already engaged as research team members at the time an application is submitted. However, the Engagement Plan should outline how patients and other stakeholders will participate as partners in various phases of the proposed research, once awarded. Applicants should describe their plan to form a Study Advisory Committee (SAC), or other appropriate engagement body, to ensure that a broad spectrum of patients and other stakeholders advise and assist the research team with refining the study questions, outcomes, and protocols. These patients and other stakeholders must include national or regional organizations that represent—at a minimum—patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders. Additional representation may be recommended in collaboration with PCORI, including individual patients with lived experience and other relevant stakeholders, such as scientific and methodological experts. The SAC or other appropriate engagement body should meet in person at least two times per year, and the budget should account for these engagement costs.

PCORI understands that engagement structures and approaches vary widely. Other engagement approaches, such as forming stakeholder groups, panels, task forces, working groups and other bodies or involving individual patient and other stakeholder partners in various ways, are also permissible to employ—either in addition to or instead of—the formation of the SAC. For clarification in your application materials and for merit review purposes, please indicate which body or structure is filling the SAC requirements, including the requirements for in-person meetings at least two times per year and appropriate budgeting.

³⁴ Available at <http://www.pcori.org/sites/default/files/Engagement-Rubric.pdf>.

³⁵ Available at <http://www.pcori.org/sites/default/files/PCORI-Sample-Engagement-Plans.pdf>.

Populations Studied

PCORI seeks to fund research that includes diverse populations with respect to age, gender, race, ethnicity, geography, or clinical status, so that possible differences in comparative effectiveness of the interventions may be examined (otherwise known as HTE). PCORI recognizes that some proposed studies might represent important PCOR opportunities, even in the absence of a broadly diverse study population. However, the burden is on the applicant in such cases to justify the study's importance in the absence of diversity. The applicant must also discuss which subgroups are most important and how they will be analyzed, including whether there will be power to examine the question of effectiveness in subgroups. PCORI is particularly interested in including previously understudied populations for whom effectiveness information is especially needed, such as hard-to-reach populations or patients with multiple conditions. Thus, comparisons should examine the impact of the strategies in various subpopulations, with attention to the possibility that the strategy's effects might differ across subpopulations. PCORI has developed the following list of priority populations to guide our research and engagement efforts:

- Racial and ethnic minority groups
- Low-income groups
- Women
- Children (age 0–17 years)
- Older adults (age 65 years and older)
- Residents of rural areas
- Individuals with special healthcare needs, including individuals with disabilities
- Individuals with multiple chronic diseases
- Individuals with rare diseases
- Individuals whose genetic makeup affects their medical outcomes
- Patients with low health literacy, numeracy, or limited English proficiency
- Lesbian, gay, bisexual, and transgender (LGBT) persons
- Veterans and members of the Armed Forces and their families

Project Budget and Duration

As noted above, PCORI has devoted up to \$19 million in total costs to this announcement. Applicants may request up to \$10 million in total direct costs for a research project period not to exceed five years (not including peer review). The maximum budget includes all research *and* peer-review-related costs (please refer to the Application Guidelines for further details). At the time of contract execution, PCORI sets aside all of the funds associated with an awarded project to be made available throughout the contract's period of performance. Obligated funding is available for the duration of the project period. Note that, in general, PCORI will not cover costs for interventions that are being compared in the

proposed study. (See Appendix 2 in the [Application Guidelines](#) for details.) In rare cases where this policy would preclude conducting a CER study that addresses the priority questions outlined in this PFA, such as research in underserved or hard-to-reach populations or settings, PCORI may consider a waiver on this policy. In such cases, the applicant will need to address the issue of scalability, sustainability, and potential for broad dissemination of the intervention beyond the project period. The applicant should demonstrate that payers and health systems will likely cover the intervention costs if study results demonstrate its effectiveness. Request for such a waiver and the accompanying justification must be made in the LOI, and PCORI staff must approve the waiver at the LOI stage before a full application is submitted.

Applicants should propose realistic budgets, project duration, and associated time lines. For those rare circumstances in which the estimated direct cost exceeds the maximum direct costs outlined in this PFA, please provide a detailed justification in your LOI that ties the extra expense to the project's success. Not all requests for additional funds will be approved. Any request for a project period longer than five years will be denied. For further information regarding PCORI's policies about allowable and unallowable costs, refer to Appendix 2 of the [Application Guidelines](#). Note that although subcontractor indirect costs are included in the prime applicant's direct-cost budget, subcontractor indirect costs are not factored when determining adherence to the PFA's direct-cost limit.

The funding mechanism for this program is a contract. Total project funding is contingent upon successful programmatic and budget performance (e.g., meeting recruitment targets). Milestones and targets, as well as possible pilot phases for the sole purpose of assessing recruitment feasibility, should be included in the budget and will be negotiated at the time of the award. Awardees will be expected to provide corroborating evidence to receive continual funding support. Some of the activities that will be considered during negotiations include:

- Developing a study protocol and procedure manual for the intervention
- Assigning roles and responsibilities to study team members for implementing the project
- Forming a SAC or other appropriate engagement body
- Obtaining clearances from all institutional and community partners, including IRB approvals
- Establishing a DSMB or providing a clear description of why a DSMB is not necessary
- Executing all subcontractor agreements
- Agreeing on eligible patient populations for study recruitment
- Identifying barriers to patient recruitment in the study and addressing these barriers effectively
- Demonstrating successful recruitment during a pilot phase (if indicated)

Refer to the [Application Guidelines](#) for a list of additional PFA-specific project milestones.

Collaboration

PCORI is particularly interested in applications that involve community and commercial organizations that can help researchers design, implement, disseminate, and sustain effective interventions. We

encourage applications that include novel collaborations with accreditation organizations, credentialing bodies, educational enterprises, patient advocacy groups, industry, professional societies, and subspecialty societies.

Protection of Human Subjects

This component (up to five pages) is included in the Research Plan Template. Describe the protection of human subjects involved in your proposed research. PCORI follows the Federal Policy for the Protection of Human Subjects ([45 CFR part 46](#)), including the Common Rule. For more detailed information, please see Section 5, titled “Human Subjects Research Policy,” in the [Supplemental Grant Application Instructions for All Competing Applications and Progress Reports](#),³⁶ which is issued by the U.S. Department of Health and Human Services. PCORI does not require that applicants comply with sections of this policy that refer to requirements for federal-wide assurance or that refer to standards for including women, minorities, and children. Awardees must also comply with appropriate state, local, and institutional regulations and guidelines pertaining to the use of human subjects in research.

PCORI requires awardees to ensure that there is a Data and Safety Monitoring Plan (DSMP), which may include the need to appoint a DSMB, as provided in the [PCORI Policy on Data and Safety Monitoring Plans for PCORI-Funded Research](#).³⁷

PCORI merit reviewers will examine plans for protection of human subjects in all applications and may provide comments regarding the plans (see [How To Evaluate Human Subjects Protections](#)³⁸). Reviewers’ comments on human subject research are not reflected in the overall application score, but PCORI staff might use them during potential funding negotiations. Final determinations about the adequacy of human subject protections rest with the IRB or international equivalent that has jurisdiction for the study.

The Awardee Institution, whether domestic or foreign, bears ultimate responsibility for safeguarding the rights and welfare of human subjects in PCORI-supported activities.

Required Education of Key Personnel on the Protection of Human Subject Participants

PCORI requires all applicants to adhere to the NIH policy on education in the protection of human subject participants in the conduct of research. This applies to all individuals listed as key personnel in the application. The policy and FAQs are available on the [NIH website](#).³⁹

Data Management and Data-Sharing Plan

PCORI encourages openness in research and making research data available for purposes of replication and reproducibility. Although not required to be submitted as a component of the research application, if an award is made, the awardee is required to develop and maintain a plan that addresses data management and data sharing of research project data in a manner that is appropriate for the nature of the research project and the types of research project data, and that is consistent with applicable privacy, confidentiality, and other legal requirements.

³⁶ See <http://grants.nih.gov/sites/default/files/supplementalinstructions.docx>.

³⁷ See <http://www.pcori.org/sites/default/files/PCORI-Policy-Data-Safety-Monitoring-Plans.pdf>.

³⁸ See <http://www.pcori.org/sites/default/files/PCORI-Checklist-for-Evaluating-Human-Subjects-Protections.pdf/>.

³⁹ See <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-054.html>.

Peer Review and Release of Research Findings

PCORI has a legislative mandate to ensure the scientific integrity of the primary research it supports and to make study findings widely available and useful to patients, clinicians, and the general public within a specific time frame. Accordingly, the Board adopted the [Process for Peer Review of Primary Research and Public Release of Research Findings](#).⁴⁰

In summary, Awardee Institutions are required to submit to PCORI for peer review a draft final research report that provides the methodological details, describes the main study results, and interprets the findings in clinical or other decisional contexts. Subject matter experts; individuals with expertise on research methodology or biostatistics; and patients, caregivers, and other healthcare stakeholders will review the draft final research report. After Awardee Institutions have responded to reviewers' comments to PCORI's satisfaction, the report will be accepted and considered final. PCORI will then prepare a 500-word abstract summarizing the study results for patients and the general public, which the Awardee Institution will review and approve.

PCORI will post the following materials on its website no later than 90 days after the draft final research report is accepted: (1) a 500-word abstract for medical professionals; (2) a standardized summary of the study results for patients and the general public; (3) a link to the study record on [ClinicalTrials.gov](#) (as applicable); and (4) ancillary information, including conflict of interest disclosures. The final research report, along with anonymized reviewer comments, will be made publicly available on the PCORI website no later than 12 months after its acceptance, except by prior mutual agreement with the Awardee Institution.

III. How To Submit an Application

Letter of Intent

Applicants should download the [Cycle 3 2016 Opioid Management LOI Template](#) from the PCORI Funding Center. They must complete the document and convert it to a PDF with a four-page limit. PCORI suggests including all references as in-text citations using American Medical Association citation style, but other citation styles are accepted. Do not upload additional documents as part of your LOI, such as Letters of Endorsement or Support, because they are not requested at this stage. Their inclusion will result in LOI rejection without review. Please visit the PCORI Funding Center for additional applicant resources, including the PFA and required templates.

Please answer all of the questions in the LOI Template. This includes the question on brief justification for the proposed cost of the study. Providing the answer "costs not to exceed \$10 million" is not sufficient. Upload your document to PCORI Online. The deadline for LOI submission is November 1, 2016, by 5 p.m. (ET).

Letter of Intent Review

LOIs are evaluated based on the following criteria:

⁴⁰ See <http://www.pcori.org/sites/default/files/PCORI-Peer-Review-and-Release-of-Findings-Process.pdf>.

- Whether the proposed topic addresses one or both of the priority research questions identified in this funding announcement
- Importance of the specific research question (comparison), as evidenced by critical gaps identified by clinical guidelines developers or recent relevant systematic reviews
- A size or scope sufficient enough to have a significant impact on patient outcomes or healthcare practices
- Clarity and credibility of the applicants' responses to the LOI questions, as well as their justification of the proposed study size, citing published estimates, including effect sizes, standard deviations, and the need for rigorous comparative analysis of important subgroups
- Prior relevant experience
- Programmatic fit and balance, considering whether the research study question and study design are compliant with requirements in this funding announcement
- Adherence to the administrative and formatting requirements listed in the Application Guidelines, specifically the four-page limit for the LOI

Only applicants whose LOIs are deemed most responsive to this PFA will be invited to submit a full application. Notification of denial or approval to submit an application will occur no later than December 2, 2016. Please refer to the [Application Guidelines](#) for information on how to submit your LOI via PCORI Online.

You are invited to submit an application based on the information provided in the LOI. Any changes to the following require PCORI approval:

- Research question(s)
- Specific aims
- Study design
- Comparators
- Principal Investigator (PI) (Contact PI and PI #2)
- Institution

If you need to change any of this information or have any questions, please email pfa@pcori.org.

Note: A PI can only submit one LOI per PFA. However, an individual listed as a PI on one LOI may be listed as and serve in another non-PI role (e.g., co-investigator, co-PI, or consultant) on other LOIs within the same PFA during the same cycle. A PI may submit multiple LOIs to different program PFAs in a cycle, but the PI must ensure that the research topics and projects are not similar. If a PI submits an LOI to multiple program PFAs, LOIs that exhibit scientific overlap or that appear to be duplicate submissions will be disqualified. PCORI will contact the PI and provide him or her with an opportunity to choose which PFA he or she would like to apply to. This applies to single- and dual-PI submissions.

Submission Dates

LOIs and applications must be submitted in accordance with the published dates and times listed in the Overview section of this document and in the [PCORI Funding Center](#).⁴¹

PCORI Online

To submit an application, you must register with [PCORI Online](#)⁴² and submit an LOI and an application for each cycle in which you are applying.

Applicant Resources

PCORI Funding Center	http://www.pcori.org/2016-Cycle-3-Opioid-Management
PCORI Online System	pcori.fluxx.io
PCORI Funding Awards	http://www.pcori.org/research-results-home

IV. Merit Review

PCORI's merit review process is designed to support the following goals:

- Identify applications that have the strongest potential to help patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders make informed decisions to improve patient outcomes.
- Implement a transparent, fair, objective, and consistent process to identify these applications.
- Elicit high-quality feedback that reflects a diversity of perspectives to ensure that the PCORI-funded research reflects the interests and views of patients and other stakeholders and those who care for them, and that it meets the criteria for scientific rigor.
- Fund projects that fill important evidence gaps and have strong implementation potential.
- Regularly evaluate and continually improve the merit review process and policies in support of PCORI's mission.

PCORI merit review is a multiphase process that includes PFA development; staff evaluation of LOIs; the review panel's preliminary review of full applications; an in-person panel discussion of a subset of full applications (identified by PCORI's Research Priority Area Program staff and based on the preliminary review and program priorities); the Selection Committee's recommendation of applications for funding; and, finally, Board award approval.

Preliminary Review

PCORI conducts rigorous merit review of the full applications it receives. Note that PCORI may eliminate applications from the review process for administrative or scientific reasons (e.g., nonresponsiveness).

⁴¹ Available at pcori.org/apply.

⁴² Available at pcori.fluxx.io.

An application may be administratively withdrawn if it is incomplete; submitted past the stated due date and time; or does not meet the formatting criteria outlined in the [Application Guidelines](#), in the PCORI templates, and in PCORI Online. An application can be scientifically withdrawn if it is not responsive to the guidelines described in this PFA, describes research that is not comparative, includes a cost-effectiveness analysis, or otherwise does not meet PCORI programmatic requirements.

PCORI Merit Review Officers (MROs) recruit each panel based on the number of areas and topics represented by invited LOIs. MROs recruit the panel chair, scientist reviewers who are subject matter experts, patient representatives, and representatives of other stakeholder groups. All panel members receive training during the review cycle to ensure that they understand the programmatic and organizational goals of review.

The table below is designed to help applicants understand how the PCORI merit review criteria align with criteria from other funding organizations with which applicants might be familiar (e.g., NIH). Though PCORI’s criteria do map to most NIH criteria, there are areas where we ask for different information (i.e., PCORI does not include a criterion that tracks to NIH’s innovation criterion, but does include criteria evaluating patient-centeredness and engagement) reflecting PCORI’s unique approach.

Crosswalk of PCORI Merit Review Criteria with NIH Criteria	
SIGNIFICANCE	<ol style="list-style-type: none"> 1. Potential for the study to fill critical gaps in evidence 2. Potential for the study findings to be adopted into clinical practice and improve delivery of care
APPROACH	<ol style="list-style-type: none"> 3. Scientific merit (research design, analysis, and outcomes) NEW 4. Investigator(s) and environment
PCORI-only Merit Review Criteria	
PATIENT-CENTEREDNESS/ENGAGEMENT	<ol style="list-style-type: none"> 5. Patient-centeredness 6. Patient and stakeholder engagement

Below are PCORI’s merit review criteria. PCORI’s merit review panels use these criteria during the preliminary and in-person review phases to evaluate and score all submitted applications and to ensure consistency and fairness in how applications are evaluated.

Criterion 1. Potential for the study to fill critical gaps in evidence:

The application should address the following questions:

- Does the application convincingly describe the clinical burden?
- Does the application identify a critical gap in current knowledge as noted in systematic reviews, guideline development efforts, or previous research prioritizations?
- Does the application identify a critical gap in current knowledge, evidenced by inconsistency in clinical practice and decision making?
- Would research findings from the study have the potential to fill these evidence gaps?

Criterion 2. Potential for the study findings to be adopted into clinical practice and improve delivery of care

The application should describe how evidence generated from this study could be adopted into clinical practice and delivery of care by others. The application should also address the following questions:

- Does the application identify who will make the decision (i.e., the decision maker) or use (i.e., the end-user) the study findings (not the intervention) this study produces, such as local and national stakeholders?
- Does the application identify potential end-users of study findings—such as local and national stakeholders—and describe strategies to engage these end-users?
- Does the application provide information that supports a demand for this kind of a study from end-users?
- Would this study’s research findings have the potential to inform decision making for key stakeholders? If so, provide an example. How likely is it that positive findings could be reproduced by others, resulting in improvements in practice and patient outcomes? Identify the potential barriers that could hinder adoption of the intervention by others.
- Does the application describe a plan for how study findings will be disseminated beyond publication in peer-review journals and at national conferences?

Criterion 3. Scientific merit (research design, analysis, and outcomes)

The application should show sufficient technical merit in the research design to ensure that the study goals will be met. The application should also address the following questions:

- Does the application describe a clear conceptual framework anchored in background literature which informs the design, key variables, and relationship between interventions and outcomes being tested?
- Does the Research Plan describe rigorous methods that demonstrate adherence to the PCORI Methodology Standards?
- Is the overall study design justified?
- Are the patient population and study setting appropriate for the proposed research question?
- Does the application provide justification that the outcome measures are validated and appropriate for the population?
- Is each of the comparators (e.g., active intervention arm and comparator arm) described clearly and well justified? If “usual care” is one of the arms, is it adequately justified and will it be sufficiently measured?
- Are the sample sizes and power estimates appropriate? Is the study design (e.g., cluster randomized design, RCT, observational study) accounted for and anticipated effect size adequately justified?

- Is the study plan feasible? Is the project time line realistic, including specific scientific and engagement milestones? Is the strategy for recruiting participants feasible? Are assumptions about participant attrition realistic, and are plans to address patient or site attrition adequate?

NEW Criterion 4. Investigator(s) and environment

This criterion should assess the appropriateness (e.g., qualifications and experience) of the investigator(s)/team and the environment's capacity (e.g., resources, facilities, and equipment) to support the proposed project. It should not be an assessment of the institution's quality.

The application should also address the following questions:

- How well qualified are the PIs, collaborators, and other researchers to conduct the proposed activities? Is there evidence of sufficient clinical or statistical expertise (if applicable)?
- Does the investigator or co-investigator have demonstrated experience conducting projects of a similar size, scope, and complexity?
- If the project is collaborative or dual-PI, do the investigators have complementary and integrated expertise? Are the leadership, governance, and organizational structures appropriate for the project?
 - (Dual-PI option only) Does the Leadership Plan adequately describe and justify PI roles and areas of responsibility?
- Is the level of effort for each team member appropriate for successfully conducting the proposed work?
- Does the application describe adequate availability of and access to facilities and resources (including patient populations, samples, and collaborative arrangements) to carry out the proposed research?
- Is the institutional support appropriate for the proposed research?

Criterion 5. Patient-centeredness

The application should demonstrate that the study focuses on improving patient-centered outcomes and employs a patient-centered research design (i.e., a design informed or endorsed by patients). *(Note: The study can be patient-centered even if the end-user is not the patient, as long as patients will benefit from the information.)*

The application should also address the following questions:

- Does the application include a thorough description about which outcomes (both benefits and harms) are important to patients, and are those outcomes included in the study plan?
- Does the application provide information that indicates that closing the evidence gap is important to patients and other stakeholders?
- Are the interventions being compared in the study available to patients now, and are they the best options for comparison (including whether they would be chosen by patients and their healthcare providers for managing the condition being studied)?

Criterion 6. Patient and stakeholder engagement

The application should demonstrate the engagement of relevant patients and other stakeholders (e.g., patients, caregivers, clinicians, policy makers, hospitals and health systems, payers [insurance], purchasers [business], industry, researchers, and training institutions) in the conduct of the study. Quality of engagement should be evaluated based on scope, form, and frequency of patient and stakeholder involvement throughout the research process.

The application should also address the following questions:

- Does the application provide a well-justified description of how the research team incorporates stakeholder involvement? Does the study include the right individuals (e.g., researchers, patients, caregivers, clinicians, policy makers, and other healthcare system stakeholders) to ensure that the projects will be carried out successfully?
- Does the application show evidence of active engagement among scientists, patients, and other stakeholders throughout the research process (e.g., formulating questions, identifying outcomes, monitoring the study, disseminating, and implementing)? Are the frequency and level of patient and stakeholder involvement sufficient to support the study goals?
- Is the proposed Engagement Plan appropriate and tailored to the study?
- Are the roles and the decision-making authority of all study partners described clearly?
- Are the organizational structure and resources appropriate to engage patients and stakeholders throughout the project?

In-Person Review

During preliminary review, all administratively and scientifically compliant applications are evaluated and scored based on PCORI's merit review criteria, including evaluation of adherence to the PCORI Methodology Standards. After PCORI completes the preliminary review, PCORI program staff members evaluate panel scores and critiques to identify a subset of applications for merit reviewers to discuss at the in-person review meeting. Not all submitted applications move forward to in-person review.

During the in-person review, merit reviewers meet to discuss applications and to clarify further the merits of the proposed research. They also identify areas for improvement. Each application is re-scored based on the content of discussion. The Panel Chair and PCORI MRO lead the in-person panel meeting and ensure that all applications receive a fair and thorough review according to the standards outlined in the PFA.

Post-Panel Review

After the in-person meeting, PCORI program staff evaluate final merit review panel scores and comments, identify duplication or synergy among funded projects, and consider the fit of applications within the programmatic vision. Program staff members then recommend projects to a Selection Committee, which includes members of the Board. The Selection Committee considers recommendations and works with staff to identify a slate of applications for possible funding based on merit review scores, programmatic balance and fit, and PCORI's strategic priorities. This slate is then proposed to the Board for consideration and approval.

In addition, PCORI evaluates applicant risk before issuing a PCORI award. Factors considered include financial stability, quality of management systems, audit findings, and past performance on PCORI awards (e.g., compliance with PCORI reporting requirements, conformance to PCORI terms and conditions on previous awards, and timely achievement of milestones). Based on the risk assessment, PCORI may impose special terms and conditions on awardees or withhold contract issuance until such business risks are mitigated. **PCORI will not award new contracts to current awardees with overdue reports (progress, interim, final, etc.) until the overdue reports have been submitted to PCORI.**

Summary Statements and Funding Recommendations

Summary statements are provided to applicants approximately two weeks before funding decisions are announced. **If an application progresses to in-person discussion**, the applicant will receive a summary statement inclusive of:

- In-person panel discussion notes
- Final average overall score
- Preliminary reviewer critiques
- Application quartile, if applicable, which provides information for applicants to understand how they did relative to other discussed applications

Summary statements for applications that do not progress to in-person discussion include only the preliminary reviewer critiques.

Funding recommendations are made by identifying meritorious applications that fit the programmatic needs and that satisfactorily address the merit review criteria while adhering to the PCORI Methodology Standards. Programs also consider the funds allotted for the current funding announcement when deciding which applications to recommend to the Board for approval. Applicants to this current cycle's PFA will receive summary statements in August 2017 and notification of the funding status of their application no later than September 2017.